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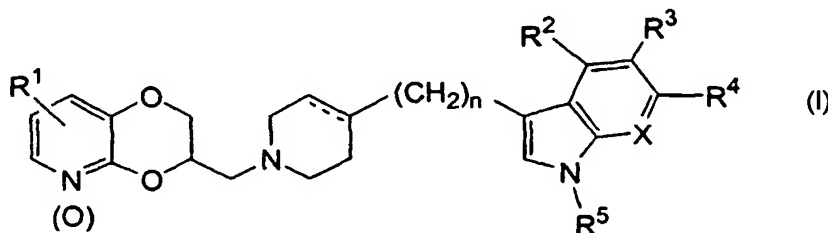
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(54) Title: ANTIDEPRESSANT AZAHETEROCYCLYLMETHYL DERIVATIVES OF 1,4-DIOXINO[2,3-b]PYRIDINE



(57) Abstract: Compounds of the formula useful for the treatment of depression, obsessive compulsive disorder, panic attacks, generalized anxiety disorder, social anxiety disorder, sexual dysfunction, eating disorders, obesity, addictive disorders caused by ethanol or cocaine abuse, and dysthymia.

ANTIDEPRESSANT AZAHETEROCYCLYLMETHYL DERIVATIVES OF 1,4-DIOXINO[2,3-b]PYRIDINE

5 This invention relates to antidepressant azaheterocyclymethyl derivatives of 1,4-dioxino[2,3-b]pyridine, to processes for preparing them, methods of using them and to pharmaceutical compositions containing them

Background of the Invention

10

Major depression is a serious health problem affecting more than 5% of the population, with a life-time prevalence of 15-20%.

15 Selective serotonin reuptake inhibitors have produced significant success in treating depression and related illnesses and have become among the most prescribed drugs. They nonetheless have a slow onset of action, often taking several weeks to produce their full therapeutic effect. Furthermore, they are effective in fewer than two-thirds of patients.

20 Serotonin selective reuptake inhibitors (SSRIs) are well known for the treatment of depression and other conditions. SSRIs work by blocking the neuronal reuptake of serotonin, thereby increasing the concentration of serotonin in the synaptic space, and thus increasing the activation of postsynaptic serotonin receptors.

 However, although a single dose of an SSRI can inhibit the neuronal serotonin transporter which would be expected to increase synaptic serotonin, long-term treatment is required before clinical improvement is achieved.

25 It has been suggested that the SSRIs increase the serotonin levels in the vicinity of the serotonergic cell bodies and that the excess serotonin activates somatodendritic autoreceptors, 5HT_{1A} receptors, causing a decrease in serotonin release in major forebrain areas. This negative feedback limits the increment of synaptic serotonin that can be induced by antidepressants.

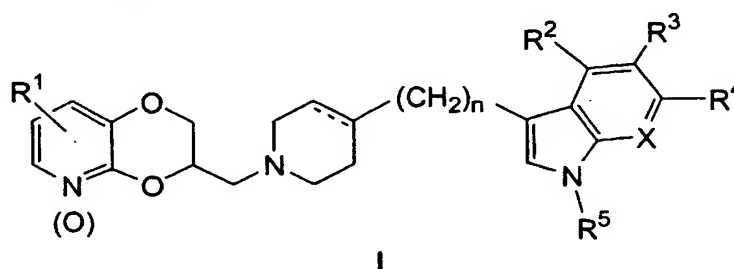
30 A 5HT_{1A} antagonist would limit the negative feedback and should improve the efficacy of the serotonin reuptake mechanism. (Perez, V., et al., *The Lancet*, 349:1594-1597 (1997)). Such a combination therapy would be expected to speed up the effect of the serotonin reuptake inhibitor.

Thus, it is highly desirable to provide improved compounds which both inhibit serotonin reuptake and which are antagonists of the 5HT_{1A} receptor.

Description of the Invention

5

In accordance with this invention, there is provided a group of novel compounds of the formula:



10 wherein

R¹ is selected from hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, trifluoromethyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms;

15

R², R³, R⁴ and R⁶ are independently selected from hydrogen, halo, cyano, trifluoromethyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, and alkanoyloxy of 2 to 6 carbon atoms; and

20

R⁵ is hydrogen or alkyl of 1 to 6 carbon atoms;

X is CR⁶ or N;

the dotted line represents an optional double bond;

(O) represents optional oxidation; and

n is an integer 0, 1 or 2;

25

or a pharmaceutically acceptable salt thereof.

In some preferred embodiments of the present invention R¹ is hydrogen, hydroxy, halo, cyano, trifluoromethyl, amino, mono- or di-alkylamino in which each

alkyl group has 1 to 6 carbon atoms, alkyl of one to six carbon atoms or alkoxy of one to six carbon atoms. In still more preferred embodiments R^1 is hydrogen.

In other preferred embodiments of the invention R^2 , R^3 and R^4 are independently selected from hydrogen, halo, cyano, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms. In still more preferred embodiments of the invention R^2 , R^3 and R^4 are independently selected from hydrogen, cyano or halogen.

In still other preferred embodiments of the invention R^3 is hydrogen or lower alkyl.

X is preferably CR^6 . When X is CR^6 , then R^6 is preferably hydrogen, halo, cyano, alkyl of one to six carbon atoms or alkoxy of one to six carbon atoms, and more preferably hydrogen, cyano or halogen.

Of the compounds of Formula I, the preferred members are those in which R^1 is attached to the 6-position of the 1,4-dioxino[2,3-b]pyridine and is hydrogen, hydroxy, halo, cyano, trifluoromethyl, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkyl of one to six carbon atoms or alkoxy of one to six carbon atoms; R^2 , R^3 and R^4 are independently selected from hydrogen, halo, cyano, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms; n is an integer 0 or 1; and R^5 , X, (O) and the dotted line are defined as above.

Most preferred are those examples in which R^1 is hydrogen, hydroxy or alkoxy of one to six carbon atoms, R^2 , R^3 and R^4 are independently selected from hydrogen, halo and cyano, R^5 is hydrogen, X is CR^6 , R^6 is hydrogen, halo, or cyano, n is 0, (O) is defined as above and the dotted line represents a double bond.

This invention relates to both the R and S stereoisomers of the 3-amino-methyl-1,4-dioxino[2,3-b]pyridines, as well as to mixtures of the R and S stereoisomers. Throughout this application, the name of the product of this invention, where the absolute configuration of the 3-aminomethyl-1,4-dioxino[2,3-b]pyridines is not indicated, is intended to embrace the individual R and S enantiomers as well as

mixtures of the two. In some embodiments of the present invention the S stereoisomer is preferred.

Where a stereoisomer is preferred, it may, in some embodiments be provided
5 substantially free of the corresponding enantiomer. Thus, an enantiomer substantially free of the corresponding enantiomer refers to a compound which is isolated or separated via separation techniques or prepared free of the corresponding enantiomer. Substantially free as used herein means that the compound is made up of a significantly greater proportion of one stereoisomer. In preferred embodiments
10 the compound is made up of at least about 90% by weight of a preferred stereoisomer. In other embodiments of the invention, the compound is made up of at least about 99% by weight of a preferred stereoisomer. Preferred stereoisomers may be isolated from racemic mixtures by any method known to those skilled in the art, including high performance liquid chromatography (HPLC) and the formation and
15 crystallization of chiral salts or prepared by methods described herein. See, for example, Jacques, et al., Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); Wilen, S.H., et al., Tetrahedron 33:2725 (1977); Eliel, E.L. Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); Wilen, S.H. Tables of Resolving Agents and Optical Resolutions p. 268 (E.L. Eliel, Ed., Univ. of
20 Notre Dame Press, Notre Dame, IN 1972).

Furthermore, it is appreciated that, when R¹ is attached to the 6-position of the 1,4-dioxino[2,3-b]pyridine and is hydroxy, the molecule may exist as either the pyridone or pyridinol tautomer. The claims in this application or intended to embrace
25 both tautomers, as well as mixtures of the two.

Alkyl as used herein refers to an aliphatic hydrocarbon chain and includes straight and branched chains such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neo-pentyl, n-hexyl, and isohexyl.
30 Lower alkyl refers to alkyl having 1 to 3 carbon atoms.

Alkanamido as used herein refers to the group R-C(=O)-NH- where R is an alkyl group of 1 to 5 carbon atoms.

Alkanoyloxy as used herein refers to the group R-C(=O)-O- where R is an alkyl group of 1 to 5 carbon atoms.

Alkanesulfonamido as used herein refers to the group $R-S(O)_2-NH-$ where R is an alkyl group of 1 to 6 carbon atoms.

Alkoxy as used herein refers to the group $R-O-$ where R is an alkyl group of 1 to 6 carbon atoms.

5 Carboxamido as used herein refers to the group $-CO-NH_2$.

Carboalkoxy as used herein refers to the group $R-O-C(=O)-$ where R is an alkyl group of 1 to 5 carbon atoms.

10 Halogen (or halo) as used herein refers to chlorine, bromine, fluorine and iodine.

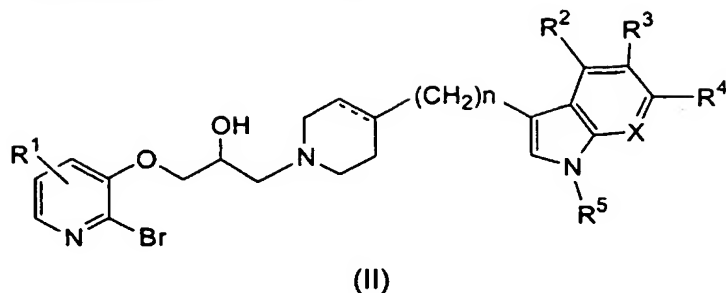
15 Pharmaceutically acceptable salts are those derived from such organic and inorganic acids as: acetic, lactic, citric, cinnamic, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, oxalic, propionic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, glycolic, pyruvic, methanesulfonic, ethanesulfonic, toluenesulfonic, salicylic, benzoic, and similarly known acceptable acids.

Specific compounds of the present invention include:

20 3-[[4-(1H-indol-3-yl)-3,6-dihydro-1(2H)-pyridinyl]methyl]-2,3-dihydro-[1,4]-dioxino[2,3-b]pyridine;
3-[[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-1(2H)-pyridinyl]methyl]-2,3-dihydro-[1,4]dioxino[2,3-b]pyridine;
3-{1-[2,3-dihydro[1,4]dioxino[2,3-b]pyridin-3-ylmethyl]-1,2,3,6-tetrahydro-4-pyridinyl}-1H-indole-5-carbonitrile; and
25 3-[[4-(6-fluoro-1H-indol-3-yl)-3,6-dihydro-1(2H)-pyridinyl]methyl]-2,3-dihydro-[1,4]dioxino[2,3-b]pyridine; and pharmaceutical salts thereof.

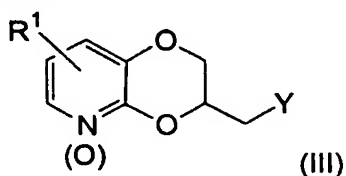
30 This invention also provide a process for preparing a compound of formula (I) as defined above or a pharmacaceutically acceptable salt thereof, which comprises one of the following:

a) cyclising a compound of formula (II):



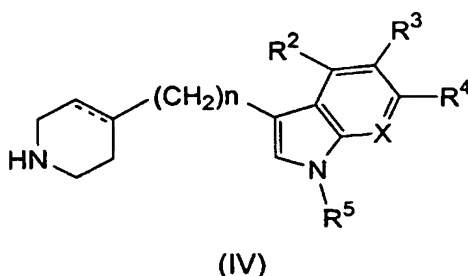
5 wherein n, X and R¹⁻⁵ and the dotted line are as defined above, eg using palladium acetate and base,
or

(b) reacting a compound of formula (III)



10

wherein R¹ is as defined above and Y is a leaving group, eg halogen or an organic sulphonyloxy group such as an alkyl- or aryl- sulphonyloxy group, eg -OTs ;
with a compound of formula (IV):



15

wherein n, X, R², R³, R⁴ and R⁵ and the dotted line are as defined above to give a compound of formula (I);

or

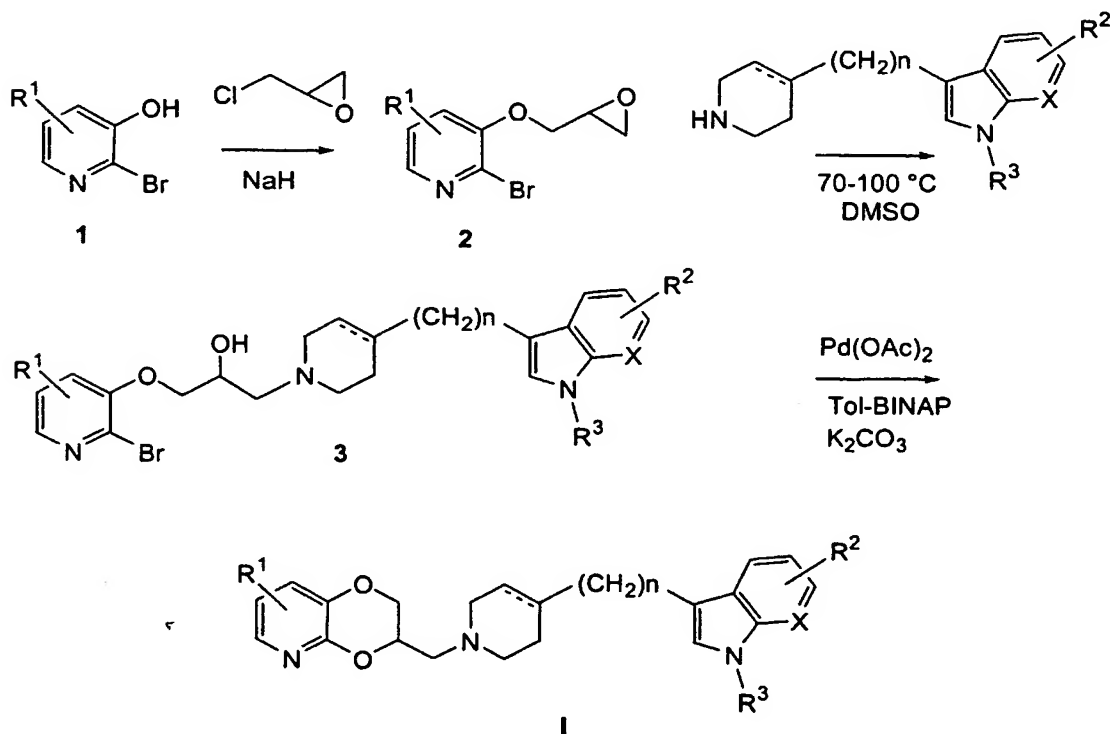
(c) converting a basic compound of formula (I) to a pharmaceutically acceptable
20 acid addition salt thereof;
or

(d) resolving an isomeric mixture of compounds of formula (I) to isolate an enantiomer of a compound of formula (I) or a pharmaceutically acceptable salt thereof; or

- 5 (e) oxidizing a compound of formula (I) as defined above wherein (O) is absent to give an N-oxide of formula (I).

The compounds of the invention are most conveniently prepared by the method outlined in Scheme I below. Unless otherwise noted, the variables are as defined above. Specifically, the appropriately substituted 2-bromo-3-pyridinol (1) is alkylated with glycidyl tosylate or nitrobenzenesulfonate or an epihalohydrin in the presence of a suitable base such as sodium hydride or potassium carbonate. The resulting glycidyl ether (2) is heated with the appropriate azaheterocycle in a high

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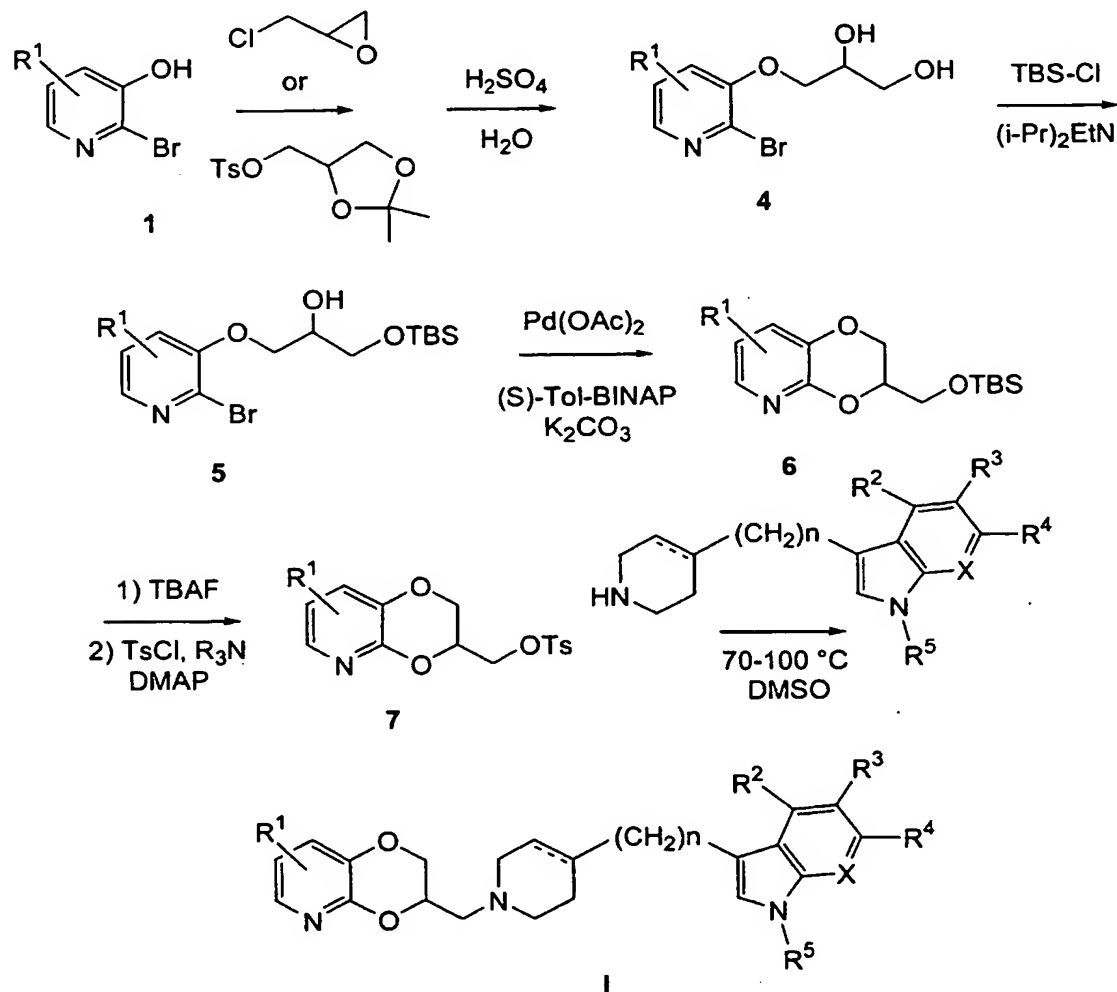
Scheme I

boiling solvent such as dimethyl sulfoxide to effect an opening of the epoxide to a vicinal amino alcohol (3). Cyclization of the secondary alcohol to the title compounds

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of the invention is accomplished by treatment with catalytic palladium acetate and 2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl [Tol-BINAP] in the presence of sodium or potassium carbonate.

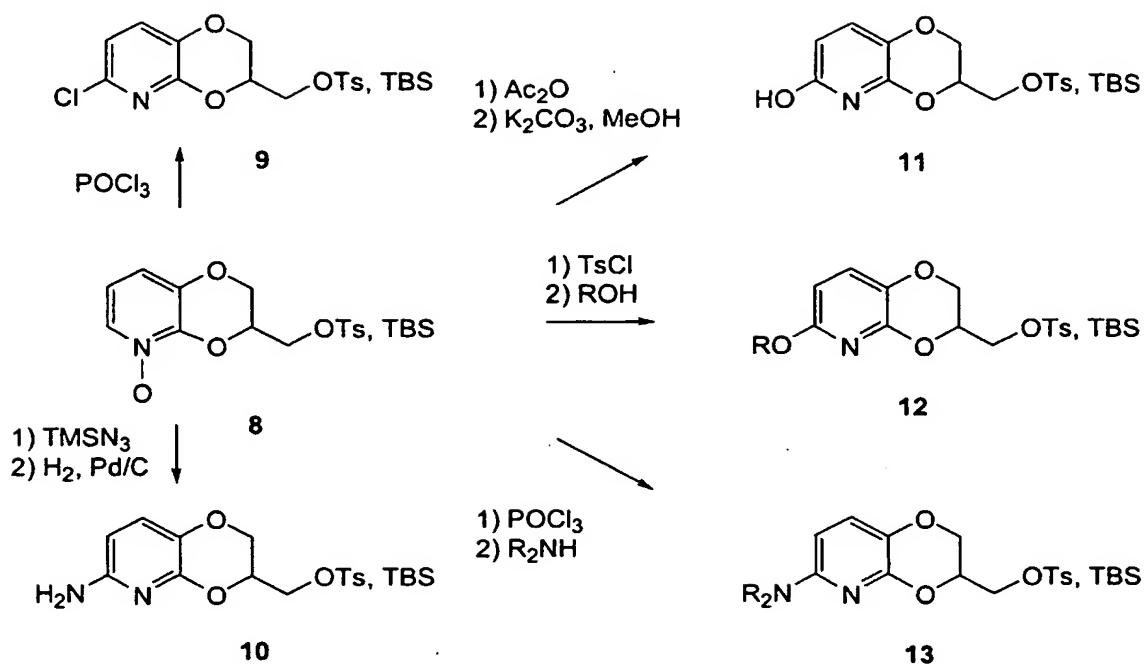
- 5 Alternatively, the appropriately substituted 2-bromo-3-pyridinol (1) may be alkylated either with an epihalohydrin or glycidyl tosylate as described above or with α,β -isopropylidene- γ -tosylate as shown in Scheme II below and then treated with dilute aqueous acid to give the vicinal diol (4). The primary alcohol is selectively protected with a suitable protecting group such as a t-butyl dimethylsilyl (TBS) ether to produce (5) and then cyclization to the pyridodioxan effected by treatment with catalytic palladium acetate and Tol-BINAP in the presence of potassium carbonate as described above to produce (6). Following deprotection of the pyridodioxan alcohol



Scheme II

via treatment with tetra-n-butylammonium fluoride (TBAF) in methanol and conversion to the tosylate with p-toluenesulfonyl chloride (TsCl) in the presence of a tertiary base and catalytic dimethylaminopyridine (DMAP) to produce (7), the title compounds of the invention are produced by reaction with the appropriate azaheterocycle in a high boiling solvent such as dimethylsulfoxide. Oxidation of the pyridodioxan-3-methyl tosylate or silyl ether with meta-chloroperoxybenzoic acid (m-CPBA) or hydrogen peroxide leads to the compounds of the invention which are pyridine-N-oxides.

10 The pyridine-N-oxide also allows convenient access to the compounds of the invention which are substituted in the 6-position as shown in Scheme III below. Treatment of the N-oxide (8) with phosphorus oxyhalide gives the 6-halo derivative (9), which can be treated with a primary or secondary amine to give the 6-mono- or dialkylamino derivatives (13), or with sodium cyanide to give the 6-nitrile. Treatment of the N-oxide with acetic anhydride, followed by hydrolysis with mild base, gives the 6-hydroxy derivative (11). Treatment of the N-oxide with p-toluenesulfonyl chloride followed by the appropriate alcohol gives the 6-alkoxy derivative (12). Treatment of the N-oxide with trimethylsilyl azide and reduction with hydrogen over palladium on carbon yields the 6-amino derivative (10). Replacement of the tosylate with the appropriately substituted azaheterocycle as described above gives the title compounds of the invention.



Scheme III

The azaheterocycles appropriate to the invention are known compounds or
 5 they can be prepared by one skilled in the art. The compounds of the invention
 may be resolved into their enantiomers by conventional methods or, preferably, they
 may be prepared directly by substitution of (2R)-(-)-glycidyl tosylate or (R)- α,β -
 isopropylidene- γ -tosylate (for the R pyridodioxan-3-methylamine) or (2S)-(+)-glycidyl
 tosylate or (S)- α,β -isopropylidene- γ -tosylate (for the S enantiomer) in place of
 10 epichlorohydrin in the procedures above.

Like the antidepressants fluoxetine, paroxetine and sertraline, the compounds
 of this invention have the ability to potently block the reuptake of the brain
 neurotransmitter serotonin. They are thus useful for the treatment of depression and
 15 other diseases commonly treated by the administration of serotonin selective reuptake
 inhibitor (SSRI) antidepressants, such as obsessive compulsive disorder, panic
 attacks, generalized anxiety disorder, social anxiety disorder, sexual dysfunction,
 eating disorders, obesity, addictive disorders caused by ethanol or cocaine abuse and
 related illnesses. Moreover, the compounds of this invention have potent affinity for
 20 and antagonist activity at brain 5-HT_{1A} serotonin receptors. Recent clinical trials

employing drug mixtures (eg, fluoxetine and pindolol) have demonstrated a more rapid onset of antidepressant efficacy for a treatment combining SSRI activity and 5-HT_{1A} antagonism (Blier and Bergeron, 1995; F. Artigas et. al., 1996; M. B. Tome et. al., 1997). The compounds of the invention are thus exceedingly interesting and
5 useful for treating depressive illnesses.

A protocol similar to that used by Cheetham et. al. (Neuropharmacol. 32:737, 1993) was used to determine the affinity of the compounds of the invention for the serotonin transporter. The compound's ability to displace ³H-paroxetine from male rat
10 frontal cortical membranes was determined using a Tom Tech filtration device to separate bound from free ³H-paroxetine and a Wallac 1205 Beta Plate[®] counter to quantitate bound radioactivity. K_i's thus determined for standard clinical antidepressants are 1.96 nM for fluoxetine, 14.2 nM for imipramine and 67.6 nM for zimelidine. A strong correlation has been found between ³H-paroxetine binding in rat
15 frontal cortex and ³H-serotonin uptake inhibition.

High affinity for the serotonin 5-HT_{1A} receptor was established by testing the claimed compound's ability to displace [³H] 8-OHDPAT (dipropylaminotetralin) from the 5-HT_{1A} serotonin receptor following a modification of the procedure of Hall et al., J.
20 Neurochem. 44, 1685 (1985) which utilizes CHO cells stably transfected with human 5-HT_{1A} receptors. The 5-HT_{1A} affinities for the compounds of the invention are reported below as K_i's.

Antagonist activity at 5-HT_{1A} receptors was established by using a ³⁵S-GTPγS
25 binding assay similar to that used by Lazareno and Birdsall (Br. J. Pharmacol. 109: 1120, 1993), in which the test compound's ability to affect the binding of ³⁵S-GTPγS to membranes containing cloned human 5-HT_{1A} receptors was determined. Agonists produce an increase in binding whereas antagonists produce no increase but rather reverse the effects of the standard agonist 8-OHDPAT. The test compound's
30 maximum inhibitory effect is represented as the I_{max}, while its potency is defined by the IC₅₀.

The results of the three standard experimental test procedures described in the preceding three paragraphs were as follows:

	5-HT Transporter Affinity		5-HT _{1A} Receptor Affinity	5-HT _{1A} Function
5	<u>Compound</u>	<u>KI (nM)</u>	<u>KI (nM)</u>	<u>IC₅₀ (nM) (I_{max})</u>
	Example 1	9.50	14.30	197.0 (62.0)
	Example 2	2.39	6.81	57.0 (94.0)
	Example 3	2.58	22.40	183.0 (100%)
	Example 4	1.21	10.16	618.0 (77.0)

10

Hence, the compounds of this invention are combined serotonin reuptake inhibitors/5-HT_{1A} antagonists and are useful for the treatment of diseases commonly treated by the administration of serotonin selective reuptake inhibitor (SSRI) anti-depressants, such as depression (including but not limited to major depressive disorder, childhood depression and dysthymia), anxiety, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder (also known as pre-menstrual syndrome), attention deficit disorder (with and without hyperactivity), obsessive compulsive disorder (including trichotillomania), social anxiety disorder, generalized anxiety disorder, obesity, eating disorders such as anorexia nervosa, bulimia nervosa, vasomotor flushing, cocaine and alcohol addiction, sexual dysfunction (including premature ejaculation), and related illnesses.

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Also encompassed by the present invention are pharmaceutical compositions for treating or controlling disease states or conditions of the central nervous system comprising at least one compound of Formula I, mixtures thereof, and or pharmaceutical salts thereof, and a pharmaceutically acceptable carrier therefore. Such compositions are prepared in accordance with acceptable pharmaceutical procedures, such as described in *Remingtons Pharmaceutical Sciences*, 17th edition, ed. Alfonso R. Gennaro, Mack Publishing Company, Easton, PA (1985). Pharmaceutically acceptable carriers are those that are compatible with the other ingredients in the formulation and biologically acceptable.

25
30

The compounds of this invention may be administered orally or parenterally, neat or in combination with conventional pharmaceutical carriers. Applicable solid

carriers can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In
5 tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium
10 carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient of this invention can be dissolved or
15 suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples
20 of liquid carriers for oral and parenteral administration include water (particularly containing additives as above e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an
25 oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous
30 injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets, capsules, powders, solutions, suspensions, emulsions, granules, or
35 suppositories. In such form, the composition is sub-divided in unit dose containing

appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package
5 form.

The amount provided to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, and the state of the patient, the manner of administration, and the like. In therapeutic
10 applications, compounds of the present invention are provided to a patient already suffering from a disease in an amount sufficient to cure or at least partially ameliorate the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as a "therapeutically effective amount." The dosage to be used in the treatment of a specific case must be subjectively determined by the
15 attending physician. The variables involved include the specific condition and the size, age and response pattern of the patient. Generally, a starting dose is about 5 mg per day with gradual increase in the daily dose to about 150 mg per day, to provide the desired dosage level in the human.

20 Provide as used herein means either directly administering a compound or composition of the present invention, or administering a prodrug, derivative or analog which will form an equivalent amount of the active compound or substance within the body.

25 The present invention includes prodrugs of compounds of Formula I. "Prodrug", as used herein means a compound which is convertible *in vivo* by metabolic means (e.g. by hydrolysis) to a compound of Formula I. Various forms of prodrugs are known in the art, for example, as discussed in Bundgaard, (ed.), Design of Prodrugs, Elsevier (1985); Widder, et al. (ed.), Methods in Enzymology, vol. 4, Academic Press
30 (1985); Krogsgaard-Larsen, et al., (ed). "Design and Application of Prodrugs, Textbook of Drug Design and Development, Chapter 5, 113-191 (1991), Bundgaard, et al., Journal of Drug Deliver Reviews, 8:1-38(1992), Bundgaard, J. of Pharmaceutical Sciences, 77:285 et seq. (1988); and Higuchi and Stella (eds.) Prodrugs as Novel Drug Delivery Systems, American Chemical Society (1975).

The following examples illustrate the production of representative compounds of this invention.

5

INTERMEDIATE 1

2-Bromo-3-[oxiranylmethoxy]pyridine

To a mixture of 25.2 g (0.145 mole) of 2-bromo-3-pyridinol and 30 g (0.22 mole) of potassium carbonate in 80 mL of N,N-dimethylformamide was added 30 g (0.13 mole) of (S)-glycidyl tosylate. The mixture was heated under nitrogen at 55-60°C for 15 hours. The solvent was then removed in vacuum and replaced with 500 mL of methylene chloride, and the solution was washed with 500 mL of water and with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuum. The residue was column chromatographed on silica gel with methylene chloride as eluant to give 17 g of the (S)-enantiomer of the title compound as a white solid.

¹H-NMR (CDCl₃): multiplet 8.01 δ (1 H); multiplet 7.22 δ (2 H); doublet of doublets 4.38 δ (1 H); multiplet 4.04 δ (1 H); multiplet 3.40 δ (1 H); multiplet 2.95 δ (1 H); multiplet 2.85 δ (1 H).

20

EXAMPLE 1

3-[4-(1H-Indol-3-yl)-3,6-dihydro-1(2H)-pyridinyl]methyl]-2,3-dihydro[1,4]dioxino[2,3-b]pyridine

3-(1,2,3,6-Tetrahydro-4-pyridinyl)-1H-indole (1.03 g, 5.22 mmole) and 2-bromo-3-[(2S)-oxiranylmethoxy]pyridine (0.80 g, 3.47 mmole) were combined in DMSO (25 mL). This solution was heated at 75-80°C under nitrogen for 5 hours. After completion, the reaction was cooled to room temperature and partitioned between 250 mL each of ethyl acetate and saturated sodium bicarbonate. The organic phase was washed with brine, dried over magnesium sulfate and concentrated in vacuum. The crude residue was column chromatographed on silica gel using first methylene chloride as eluant to remove impurities and then 3% methanol in methylene chloride to elute the product, which upon concentration in vacuum, gave a yellow solid (1.05 g, 71%). 0.55 g (1.28 mmole) of this yellow intermediate was then cyclized in toluene (50 mL) in the presence of palladium (II) acetate (0.015 g, 0.061 mmole), (S)-(-)-2,2'-

bis(di-p-tolylphosphino)-1,1'-binaphthyl (0.052 g, 0.077 mmole), and potassium carbonate (0.21 g, 1.5 mmol). The heterogeneous mixture was heated to 100°C for a period of 24 hours. After the mixture cooled to room temperature, the catalysts were removed by filtration and the filtrate was concentrated to a crude brown oil, which was then column chromatographed on silica gel with 3% methanol in methylene chloride as eluant to give the desired product as a brown oil (0.23 g, 52%). The oil was crystallized from ethanol with the addition of a solution of oxalic acid (0.04 g) in hot ethanol to give 0.10 g of the (S)-enantiomer of the title compound as a yellow solid oxalate, m.p. 116°C.

Elemental Analysis for: $C_{21}H_{21}N_3O_2 \cdot C_2H_2O_4 \cdot H_2O$

Calc'd: C, 60.65; H, 5.53; N, 9.23

Found: C, 60.94; H, 5.32; N, 8.89

EXAMPLE 2

3-{[4-(5-Fluoro-1H-indol-3-yl)-3,6-dihydro-1(2H)-pyridinyl]methyl}-2,3-dihydro{1,4]dioxino[2,3-b]pyridine

5-Fluoro-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole (1.16 g, 5.37 mmole) and 2-bromo-3-[(2S)-oxiranylmethoxy]pyridine (0.83 g, 3.6 mmole) were combined in DMSO (40 mL). This solution was heated at 75-80°C under nitrogen for 5 hours. After completion, the reaction was cooled to room temperature and partitioned between 250 mL each of ethyl acetate and saturated sodium bicarbonate. The organic phase was washed with brine, dried over magnesium sulfate and concentrated in vacuum. The crude residue was column chromatographed on silica gel using first methylene chloride as eluant to remove impurities and then 3% MeOH/CH₂Cl₂ to elute the product, which was a yellow solid (0.90 g, 56%). The intermediate (0.90 g, 2.01 mmole) was then cyclized in toluene (40 mL) in the presence of palladium (II) acetate (0.02 g, 0.09 mmole), (S)-(-)-2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl (0.085 g, 0.12 mmole), and potassium carbonate (0.33 g, 2.4 mmole). The heterogeneous mixture was heated to 100 °C for a period of 24 hours. After the mixture cooled to room temperature, the catalysts were removed by filtration and the filtrate was concentrated in vacuum. The resulting crude brown oil was then column chromatographed on silica gel with 3% methanol in methylene chloride to give the desired product as a brown oil (0.23 g, 33%). The oil was crystallized from ethanol

with the addition of a solution of oxalic acid (0.05 g) in hot ethanol to give 0.24 g of the (S)-enantiomer of the title compound as a white solid hemioxalate, m.p. 124°C.

Elemental Analysis for: $C_{21}H_{20}FN_3O_2 \cdot 0.50 C_2H_2O_4 \cdot H_2O$

Calc'd: C, 61.68; H, 5.41; N, 9.80

5 Found: C, 61.96; H, 5.02; N, 9.80

EXAMPLE 3

3-{1-[2,3-Dihydro[1,4]dioxino[2,3-b]pyridin-3-ylmethyl]-1,2,3,6-tetrahydro-4-pyridinyl}-1H-indole-5-carbonitrile

10

3-(1,2,3,6-Tetrahydro-4-pyridinyl)-1H-indole-5-carbonitrile (1.62 g, 7.26 mmole) and 2-bromo-3-[(2S)-oxiranylmethoxy]pyridine (0.84 g, 3.65 mmol) were combined in DMSO (40 mL). This solution was heated at 75-80°C under nitrogen for 5 hours. After completion, the reaction was cooled to room temperature and partitioned
15 between 250 mL each of ethyl acetate and saturated sodium bicarbonate. The organic phase was washed with brine, dried over magnesium sulfate and concentrated in vacuum. The crude residue was column chromatographed on silica gel using first methylene chloride as eluant to remove impurities and then 3% methanol in methylene chloride to elute the product, which was a yellow foam (0.30 g,
20 18%). The intermediate (0.30 g, 0.66 mmole) was then cyclized in toluene (40 mL) in the presence of palladium (II) acetate (0.015 g, 0.067 mmole), (S)-(-)-2,2'-Bis(di-p-tolylphosphino)-1,1'-binaphthyl (0.032 g, 0.047 mmole), and potassium carbonate (0.13 g, 0.94 mmole). The heterogeneous mixture was heated at 100°C for a period of 30 hours. After the mixture cooled to room temperature, the catalysts were
25 removed by filtration and the filtrate was concentrated in vacuum. The resulting crude brown oil was then column chromatographed on silica gel with 3% methanol in methylene chloride to give the desired product as a brown oil (0.100 g, 42%). The oil was crystallized from ethanol with the addition of a solution of oxalic acid in hot ethanol to give 0.050 g of the (S)-enantiomer of the title compound as a white solid,
30 m.p. 165°C.

Elemental Analysis for: $C_{22}H_{20}N_4O_2 \cdot 1.4 C_2H_2O_4$

Calc'd: C, 59.76; H, 5.61; N, 11.24

Found: C, 59.77; H, 4.95; N, 10.89

EXAMPLE 4**3-[[4-(6-Fluoro-1H-indol-3-yl)-3,6-dihydro-1(2H)-pyridinyl]methyl]-2,3-dihydro[1,4]dioxino[2,3-b]pyridine**

5 6-Fluoro-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole (1.87 g, 8.65 mmole) and
2-bromo-3-[(2S)-oxiranylmethoxy]pyridine (1.00 g, 4.34 mmole) were combined in
DMSO (45 mL). This solution was heated at 75-80°C under nitrogen for 5 hours. After
completion, the reaction was cooled to room temperature and partitioned between 250
10 mL each of ethyl acetate and saturated sodium bicarbonate. The organic phase was
washed with brine, dried over magnesium sulfate and concentrated in vacuum. The
crude oil was column chromatographed on silica gel using first methylene chloride as
eluant to remove impurities and then 3% methanol in methylene chloride to elute the
product, which was a yellow solid (0.30 g, 15%). The intermediate (0.30 g, 0.67
15 mmole) was then cyclized in toluene (40 mL) in the presence of palladium (II) acetate
(0.010 g, 0.044 mmole), (S)-(-)-2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl (0.030 g,
0.044 mmole), and potassium carbonate (0.11 g, 0.80 mmole). The heterogeneous
mixture was heated at 100°C for a period of 24 hours. After the mixture cooled to
room temperature, the catalysts were removed by filtration and the filtrate was
concentrated in vacuum. The resulting crude brown oil was then column
20 chromatographed on silica gel with 3% methanol in methylene chloride to give the
desired product as a brown oil (0.19 g, 79%). The oil was crystallized from ethanol
with the addition of a solution of oxalic acid in hot ethanol to give 0.070 g of the (S)-
enantiomer of the title compound as beige solid dioxalate, m.p. 120°C.

Elemental Analysis for: $C_{21}H_{20}FN_3O_2 \cdot 2 C_2H_2O_4$

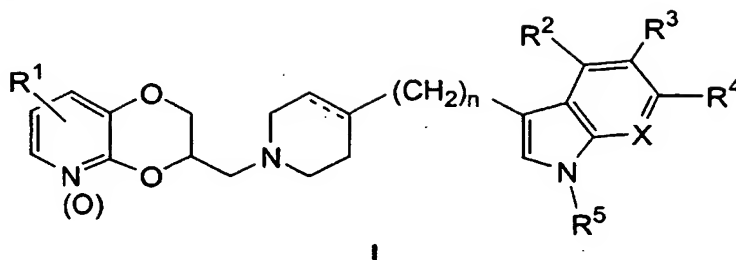
25 Calc'd: C, 55.05; H, 4.43; N, 7.70

Found: C, 55.40; H, 4.42; N, 7.48

CLAIMS

What is claimed is:

- 5 (1) A compound of formula I



wherein

- 10 R^1 is selected from hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, trifluoromethyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms;
- 15 R^2 , R^3 , R^4 and R^6 are independently selected from hydrogen, halo, cyano, trifluoromethyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, and alkanoyloxy of 2 to 6 carbon atoms; and
- R^5 is hydrogen or alkyl of 1 to 6 carbon atoms;
- X is CR^6 or N;
- 20 A dotted line represents an optional double bond;
- (O) represents optional oxidation; and
- n is an integer 0, 1 or 2;
- or a pharmaceutically acceptable salt thereof
- 25 (2) A compound according to Claim 1 wherein R^1 is hydrogen, hydroxy, halo, cyano, trifluoromethyl, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkyl of one to six carbon atoms or alkoxy of one to six carbon atoms.
- 30 (3) A compound according to Claim 1 wherein R^1 is hydrogen.

- (4) A compound according to any one of Claims 1 to 3 wherein R², R³ and R⁴ are independently selected from hydrogen, halo, cyano, alkyl of one to six carbon atoms, and alkoxy of one to six carbon atoms.
- 5
- (5) A compound according to any one of Claims 1 to 3 wherein R², R³ and R⁴ are independently selected from hydrogen, halogen, and cyano.
- (6) A compound according to any one of claims 1 to 4 wherein R⁵ is hydrogen or
10 lower alkyl.
- (7) A compound according to any one of claims 1 to 6 wherein X is CR⁶.
- (8) A compound according to Claim 7 wherein R⁶ is hydrogen, halogen or cyano.
- 15
- (9) A compound according to any one of claims 1 to 8 wherein n is an integer 0 or 1.
- (10) A compound according to any one of claims 1 to 7 in which R¹ is attached to
20 the 6-position of the 1,4-dioxino[2,3-b]pyridine.
- (11) A compound of Claim 1 in which R¹ is attached to the 6-position of the 1,4-dioxino[2,3-b]pyridine and is hydrogen, hydroxy, halo, cyano, trifluoromethyl, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkyl of
25 one to six carbon atoms or alkoxy of one to six carbon atoms; R², R³ and R⁴ are independently selected from hydrogen, halo, cyano, alkyl of one to six carbon atoms, and alkoxy of one to six carbon atoms; n is an integer 0 or 1; or a pharmaceutically acceptable salt thereof.
- 30 (12) A compound of Claim 1 in which R¹ is attached to the 6-position of the 1,4-dioxino[2,3-b]pyridine and is hydrogen, hydroxy or alkoxy of one to six carbon atoms, R², R³ and R⁴ are independently selected from hydrogen, halo and cyano, R⁵ is

hydrogen, X is CR⁶, n is 0, and the dotted line represents a double bond; or a pharmaceutically acceptable salt thereof.

(13) A compound of Claim 12 wherein R⁶ is hydrogen, halo or cyano.

5

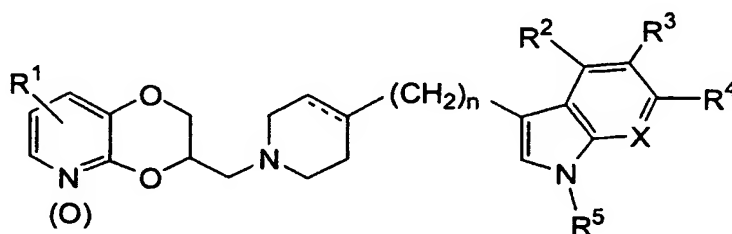
(14) The compound of Claim 1 which is 3-{{4-(1H-indol-3-yl)-3,6-dihydro-1(2H)-pyridinyl}methyl}-2,3-dihydro[1,4]dioxino[2,3-b]pyridine or a pharmaceutically acceptable salt thereof.

10 (15) The compound of Claim 1 which is 3-{{4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-1(2H)-pyridinyl}methyl}-2,3-dihydro[1,4]dioxino[2,3-b]pyridine or a pharmaceutically acceptable salt thereof.

15 (16) The compound of Claim 1 which is 3-{1-[2,3-dihydro[1,4]dioxino[2,3-b]pyridin-3-ylmethyl]-1,2,3,6-tetrahydro-4-pyridinyl}-1H-indole-5-carbonitrile or a pharmaceutically acceptable salt thereof.

20 (17) The compound of Claim 1 which is 3-{{4-(6-fluoro-1H-indol-3-yl)-3,6-dihydro-1(2H)-pyridinyl}methyl}-2,3-dihydro[1,4]dioxino[2,3-b]pyridine or a pharmaceutically acceptable salt thereof.

25 (18) A method of treating a subject suffering from a condition selected from depression, anxiety, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, attention deficit disorder, obsessive compulsive disorder, social anxiety disorder, generalized anxiety disorder, obesity, eating disorders such as anorexia nervosa, bulimia nervosa, vasomotor flushing, cocaine and alcohol addiction, and sexual dysfunction which comprises providing to the subject suffering from said condition, a therapeutically effective amount of a compound of formula I



30

wherein

5 R^1 is selected from hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, trifluoromethyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms;

10 R^2 , R^3 , R^4 and R^6 are independently selected from hydrogen, halo, cyano, trifluoromethyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, and alkanoyloxy of 2 to 6 carbon atoms; and

R^5 is hydrogen or alkyl of 1 to 6 carbon atoms;

X is CR^6 or N ;

A dotted line represents an optional double bond;

(O) represents optional oxidation; and

15 n is an integer 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

(19) The method of Claim 18 wherein the condition is depression.

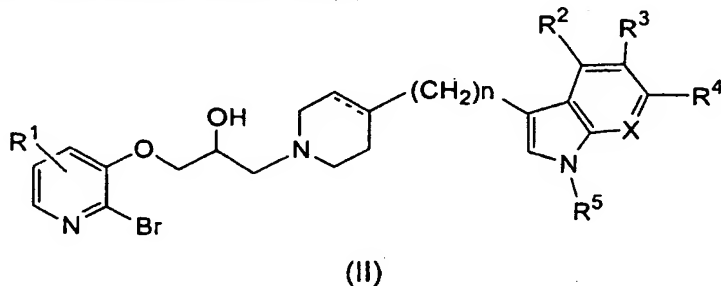
20 (20) The method of Claim 18 wherein the condition is obsessive compulsive disorder, panic attacks, generalized anxiety disorder or social anxiety disorder.

(21) A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I as claimed in any one of claims 1 to 17 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

25

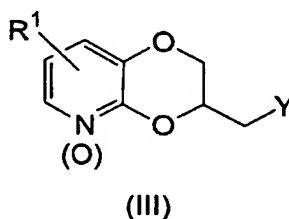
(22) A process for preparing a compound of formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt thereof, which comprises one of the following:

a) cyclising a compound of formula (II):

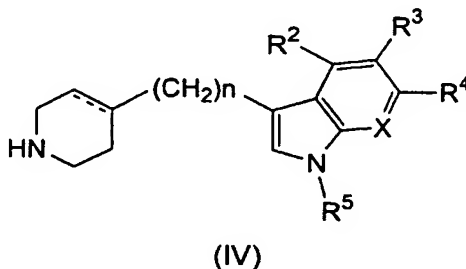


wherein n , X and R^{1-5} are as defined in claim 1, or

(b) reacting a compound of formula (III)



wherein R^1 is as defined in claim 1 and Y is a leaving group, eg halogen or an organic sulphonyloxy group such as an alkyl- aryl- sulphonyloxy group with a compound of formula (IV):



wherein n , X , R^2 , R^3 , R^4 and R^5 are as defined in claim 1;

or

(c) converting a basic compound of formula (I) to a pharmaceutically acceptable acid addition salt thereof;

20

or

- (d) resolving an isomeric mixture of compounds of formula (I) to isolate an enantiomer of a compound of formula (I) or a pharmaceutically acceptable salt thereof; or
- 5
- (e) oxidizing a compound of formula (I) as defined in claim 1 wherein (O) is absent to give an N-oxide of formula (I).

INTERNATIONAL SEARCH REPORT

In International Application No

PCT/US 02/12847

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D491/04 C07D491/056 A61K31/357 A61K31/445 A61K31/475
A61P25/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 07274 A (BOOTS CO PLC ;HEAL DAVID JOHN (GB); KERRIGAN FRANK (GB); MARTIN KE) 16 March 1995 (1995-03-16) * see the definition of Q and T * the whole document	1-22
Y	BIRCH, A.M. ET AL.: "N-Substituted (2,3-Dihydro-1,4-benzodioxin-2-yl)methylamine Derivatives as D2 Antagonists/5-HT1A Partial Agonists with Potential as Atypical Antipsychotic Agents" J.MED.CHEM., vol. 42, no. 17, 1999, pages 3342-3355, XP001084074 WASHINGTON * see p.3342, MKC-242, p.3344/45, table 1, cpd. 8,9, 22 * the whole document	1-22



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

21 June 2002

Date of mailing of the international search report

03/07/2002

Name and mailing address of the ISA

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Authorized officer

Stellmach, J

INTERNATIONAL SEARCH REPORT

In: International Application No
PCT/US 02/12847

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 24596 A (JANSSEN PHARMACEUTICA NV ;LOMMEN GUY ROSALIA EUGENE VAN (BE); ANDR) 15 August 1996 (1996-08-15) * see claim 1, definition of Q * the whole document ---	1-22
Y	EP 0 559 285 A (AKZO NV) 8 September 1993 (1993-09-08) * see claim 1 * the whole document ---	1-22
Y	EP 0 648 767 A (MERCK PATENT GMBH) 19 April 1995 (1995-04-19) * see claim 1, definition of R1 and Z * the whole document ---	1-22
Y	WO 01 14330 A (TULP MARTINUS T M ;VLIET BERNARD J VAN (NL); HES ROELOF VAN (NL);) 1 March 2001 (2001-03-01) * structural isomers * the whole document ---	1-22
Y	WO 99 05140 A (MIKKELSEN IVAN ;LUNDBECK & CO AS H (DK); MOLTZEN EJNER KNUD (DK);) 4 February 1999 (1999-02-04) * see claim 1, A = (IV), structural isomers * the whole document ---	1-22
P,X	WO 01 49680 A (KROG JENSEN CHRISTIAN ;ROTTLAENDER MARIO (DK); ANDERSEN KIM (DK);) 12 July 2001 (2001-07-12) * see claim 1, definition of X and R2-R6 * the whole document -----	1-22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/12847

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18 - 20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/US 02/12847

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9507274	A	16-03-1995	AT 191214 T	15-04-2000
			AU 689802 B2	09-04-1998
			AU 7692894 A	27-03-1995
			BG 63272 B1	31-08-2001
			BG 100388 A	31-07-1996
			BR 9407413 A	12-11-1996
			CA 2170056 A1	16-03-1995
			CN 1133043 A ,B	09-10-1996
			CZ 9600614 A3	11-09-1996
			DE 69423767 D1	04-05-2000
			DE 69423767 T2	20-07-2000
			DK 717739 T3	10-07-2000
			WO 9507274 A1	16-03-1995
			EP 0717739 A1	26-06-1996
			ES 2144528 T3	16-06-2000
			FI 961016 A	05-03-1996
			GR 3033575 T3	29-09-2000
			HU 75875 A2	28-05-1997
			IL 110844 A	28-10-1999
			JP 9502431 T	11-03-1997
			NO 960888 A	05-03-1996
			NZ 273581 A	27-05-1998
			PL 313347 A1	24-06-1996
			PT 717739 T	31-07-2000
			RO 116811 B1	29-06-2001
			RU 2136680 C1	10-09-1999
			SI 9420058 A ,B	31-12-1996
			SK 27196 A3	01-10-1996
			US 5767116 A	16-06-1998
			ZA 9406798 A	06-04-1995
WO 9624596	A	15-08-1996	AU 692361 B2	04-06-1998
			AU 4785696 A	27-08-1996
			CA 2211889 A1	15-08-1996
			WO 9624596 A1	15-08-1996
			EP 0808316 A1	26-11-1997
			FI 973245 A	06-08-1997
			IL 117045 A	12-03-1999
			JP 10513460 T	22-12-1998
			NO 973624 A	06-08-1997
			TW 446706 B	21-07-2001
			US 5990123 A	23-11-1999
			ZA 9600933 A	06-08-1997
EP 0559285	A	08-09-1993	AU 3395293 A	09-09-1993
			CA 2090767 A1	07-09-1993
			EP 0559285 A1	08-09-1993
			FI 930964 A	07-09-1993
			JP 6009641 A	18-01-1994
			MX 9301235 A1	01-09-1993
			NO 930822 A	07-09-1993
			ZA 9301343 A	24-09-1993
EP 0648767	A	19-04-1995	DE 4333254 A1	06-04-1995
			AT 153663 T	15-06-1997
			AU 679774 B2	10-07-1997
			AU 7424494 A	13-04-1995
			BR 1100891 A3	06-06-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/12847

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0648767 A		CA 2133152 A1	31-03-1995
		CN 1106811 A ,B	16-08-1995
		CZ 9402370 A3	12-04-1995
		DE 59402902 D1	03-07-1997
		DK 648767 T3	22-12-1997
		EP 0648767 A1	19-04-1995
		ES 2105454 T3	16-10-1997
		GR 3024551 T3	31-12-1997
		HU 71833 A2	28-02-1996
		JP 7149762 A	13-06-1995
		NO 943616 A	31-03-1995
		PL 305216 A1	03-04-1995
		RU 2132848 C1	10-07-1999
		SK 118494 A3	10-05-1995
		US 5532241 A	02-07-1996
		ZA 9407622 A	16-05-1995
WO 0114330 A	01-03-2001	AU 7411800 A	19-03-2001
		BR 0013498 A	14-05-2002
		WO 0114330 A2	01-03-2001
		EP 1212320 A2	12-06-2002
		NO 20020810 A	19-02-2002
WO 9905140 A	04-02-1999	AU 736596 B2	02-08-2001
		AU 8534098 A	16-02-1999
		BG 104148 A	31-05-2001
		BR 9810790 A	25-07-2000
		CN 1265107 T	30-08-2000
		WO 9905140 A1	04-02-1999
		EP 1007523 A1	14-06-2000
		HU 0002830 A2	28-09-2001
		NO 20000372 A	21-03-2000
		NZ 502252 A	28-09-2001
		PL 338194 A1	09-10-2000
		SK 952000 A3	12-03-2001
		TR 200000231 T2	21-07-2000
		ZA 9806237 A	31-03-1999
WO 0149680 A	12-07-2001	AU 2352101 A	16-07-2001
		WO 0149680 A1	12-07-2001